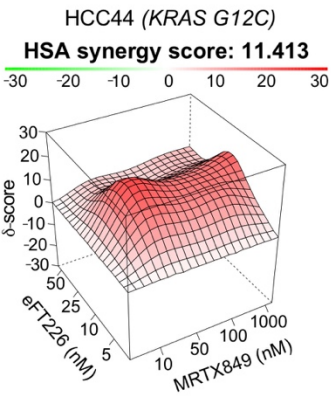
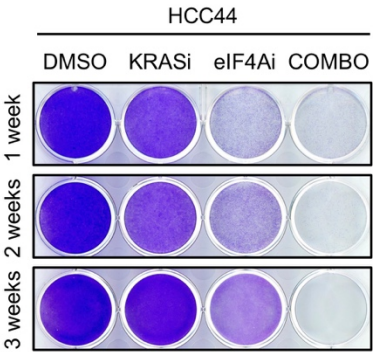


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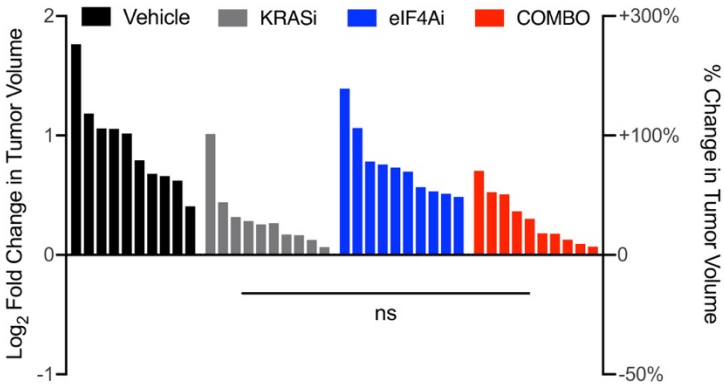


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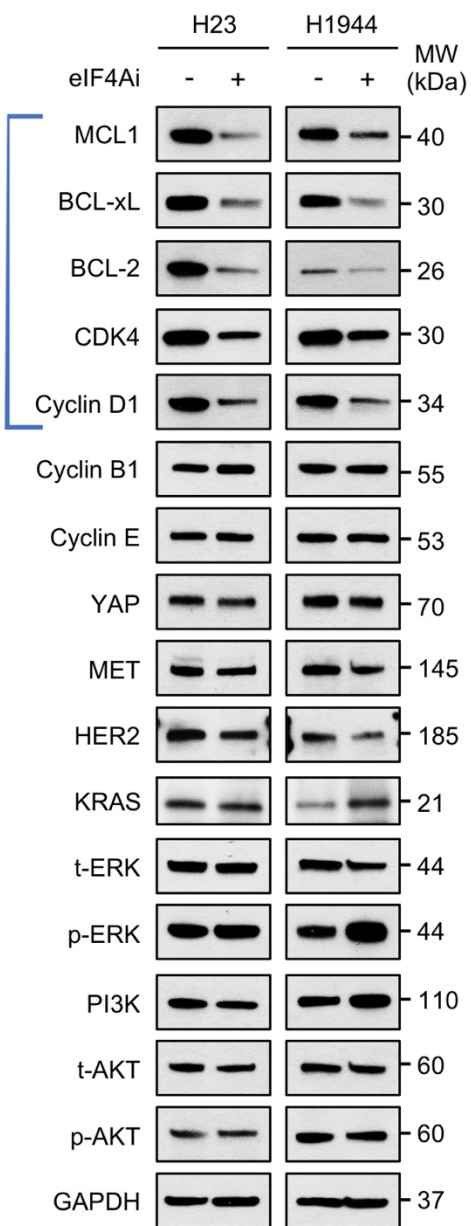


Supplemental Figure 1. eIF4A and KRAS G12C inhibitors synergize and cause durable cytotoxic responses in NSCLC cells. (A) Synergy plot depicting the effects of eFT226 and MRTX849 using the HSA model in HCC44 cells. (B) Long-term cell proliferation assay of HCC44 cells treated with vehicle (DMSO), 25 nM eFT226 (eIF4Ai), 100 nM MRTX849 (KRASi), or drug combinations (COMBO) up to 3 weeks.

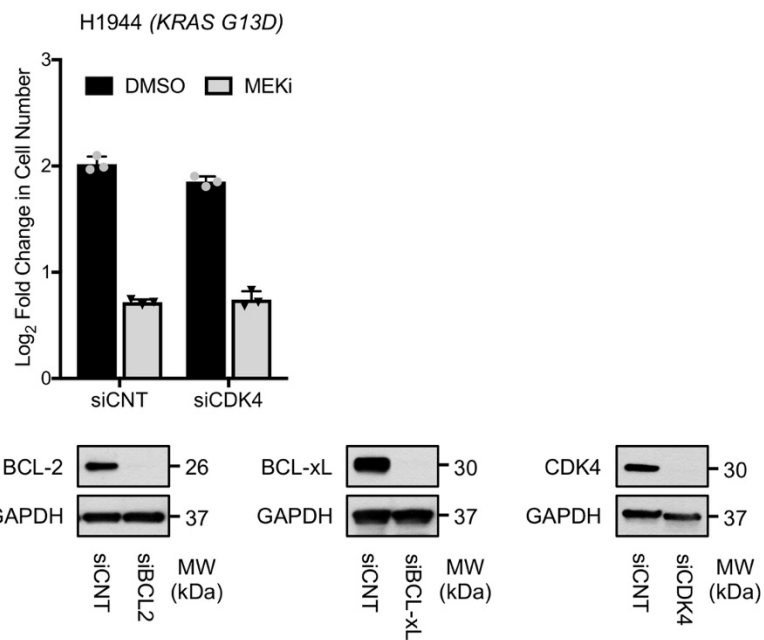
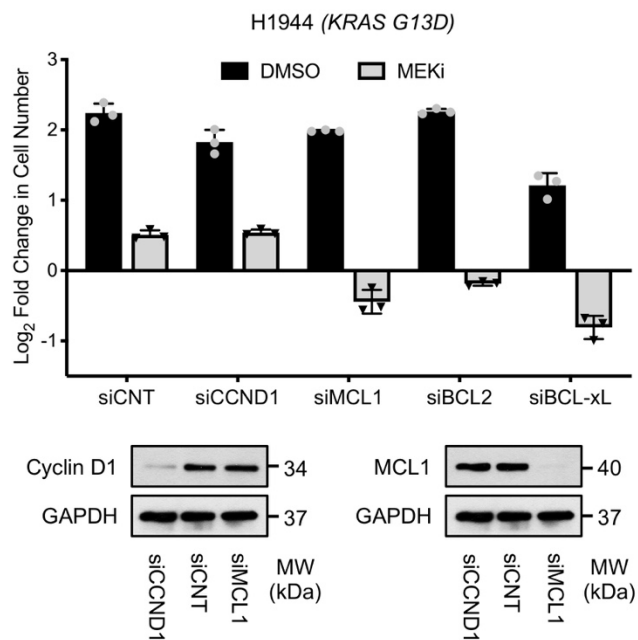
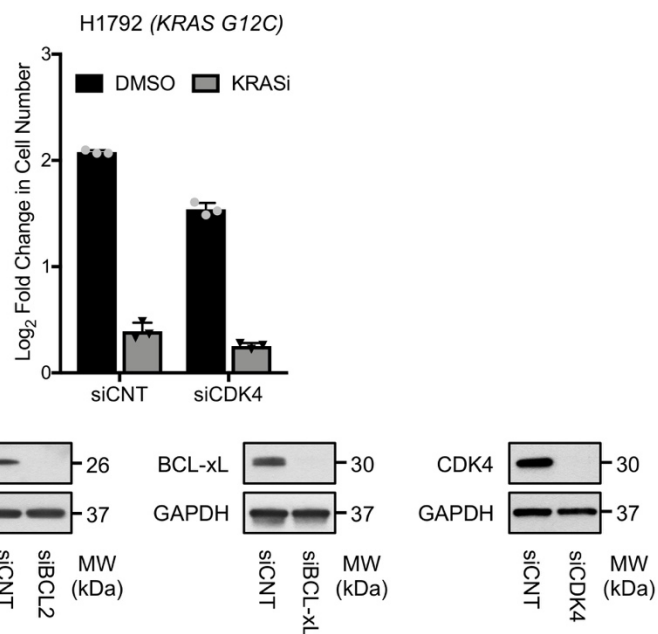
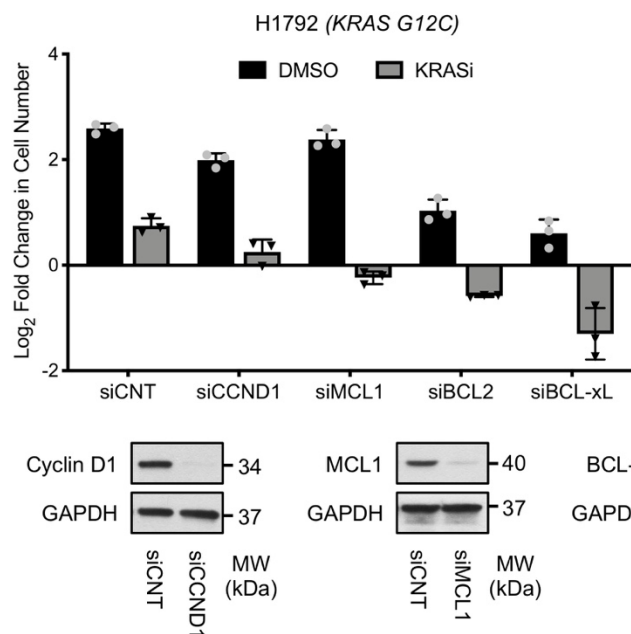
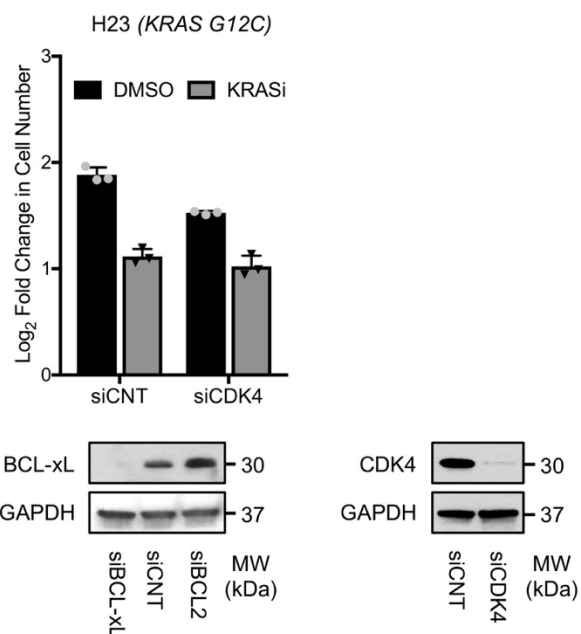
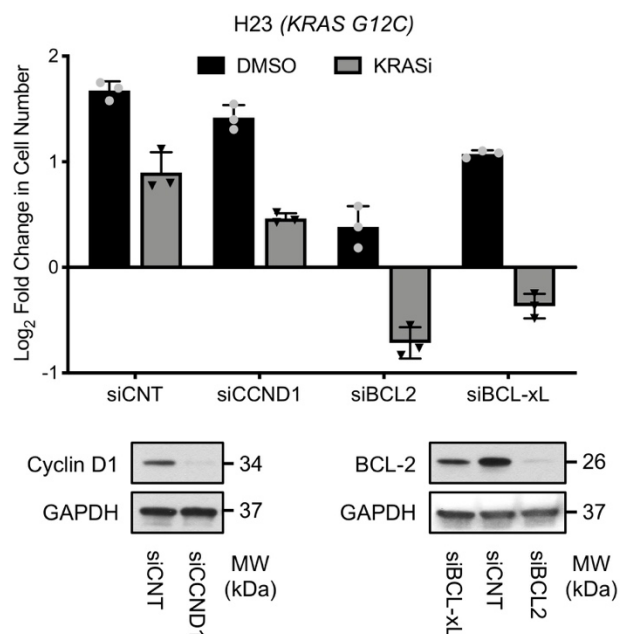
H2030 (*KRAS G12C*) xenograft model (RESISTANT)



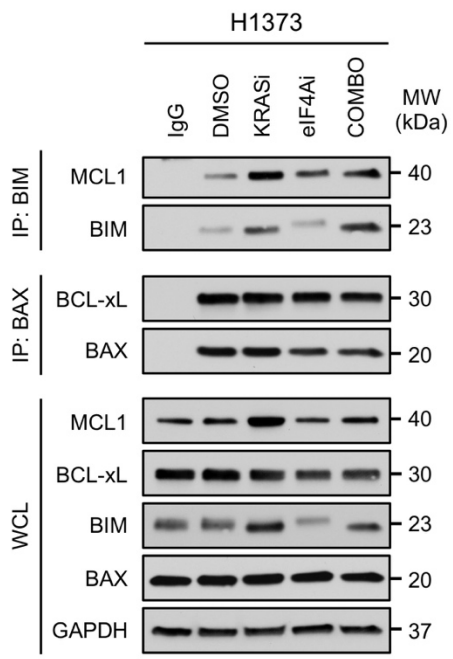
Supplemental Figure 2. Combined eIF4A and KRAS G12C inhibitors do not cause tumor regression in resistant xenograft models. Waterfall plot depicting fold-change of each tumor in resistant H2030-derived xenograft models treated for 14 days with vehicle, 100 mg/kg QD MRTX849 (KRASi), 0.5 mg/kg Q4D eFT226 (eIF4Ai), or the two agents together (COMBO) (versus day 0) (ns, not significant; one-way ANOVA and Tukey's post hoc test).



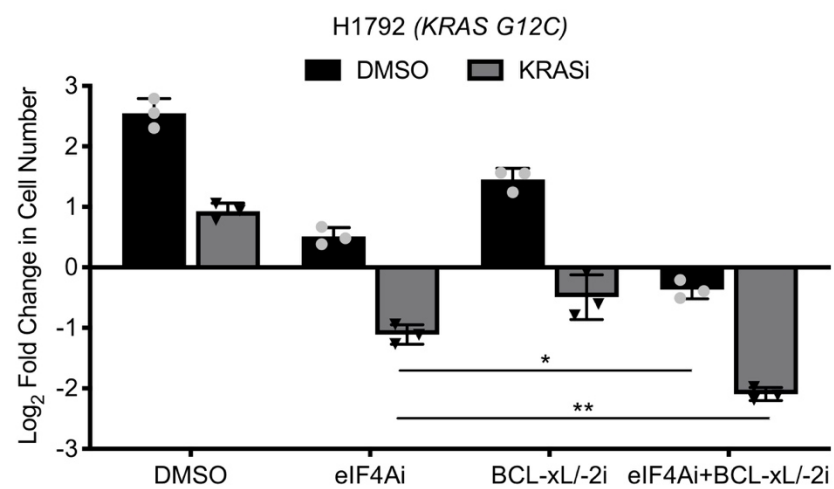
Supplemental Figure 3. eIF4A inhibitors suppress the expression of pro-survival BCL-2 family proteins, Cyclin D1, and CDK4 in sensitive NSCLCs. Immunoblots showing the protein expression of established eIF4A-regulated candidates in H23 and H1944 sensitive lines after 24 hours of treatment with vehicle (DMSO) or eFT226 (eIF4Ai). Bracket indicates the targets to be further investigated.



Supplemental Figure 4. Suppression of the pro-survival proteins is required to trigger cell death when combined with KRAS G12C or MEK inhibitors. Bar graph depicting fold-change in cell number of sensitive H23, H1792, and H1944 cells where specified genes were individually knocked down via siRNAs and cells were treated for 72 hours with either 100 nM MRTX849 (KRASi) or 50 nM trametinib (MEKi) (mean \pm SD, $n = 3$).

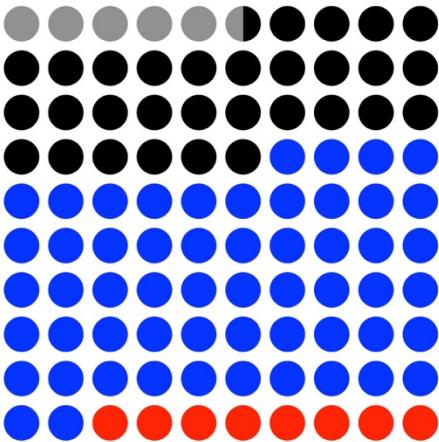


Supplemental Figure 5. Inhibition of eIF4A does not affect apoptotic signaling in resistant cells. Immunoblots showing interactions of MCL1 and BCL-xL with immunoprecipitated pro-apoptotic BIM and BAX proteins, respectively, in response to specified drug treatments in resistant H1373 cells (WCL, whole cell lysate; IP, immunoprecipitation).



Supplemental Figure 6. Relative effects of different eIF4A inhibitor-based combinations. Bar graph depicting fold-change in cell number of H1792 cells treated for 72 hours (versus day 0) with 25 nM eFT226 (eIF4Ai) \pm 1 μ M Navitoclax (BCL-xL/BCL-2i) \pm 100 nM MRTX849 (KRASi) (mean \pm SD, $n = 3$; * $p < 0.05$, ** $p < 0.01$; one-way ANOVA and Tukey's post hoc test).

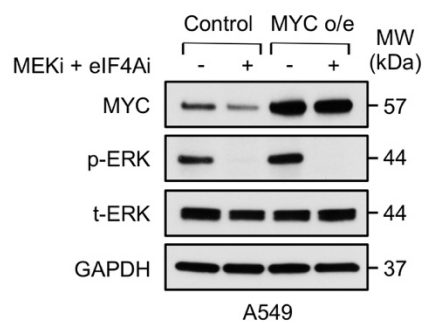
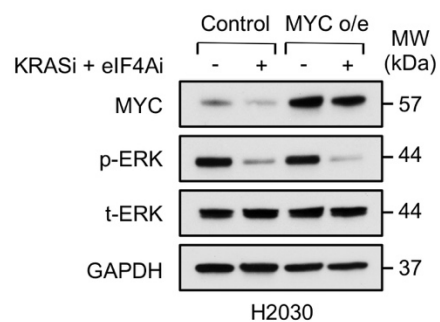
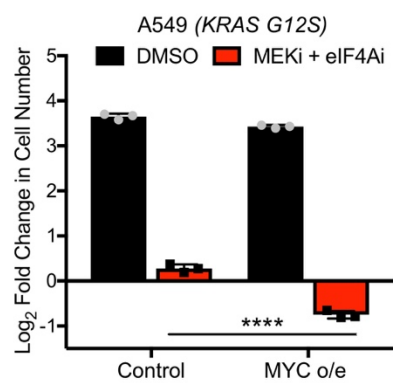
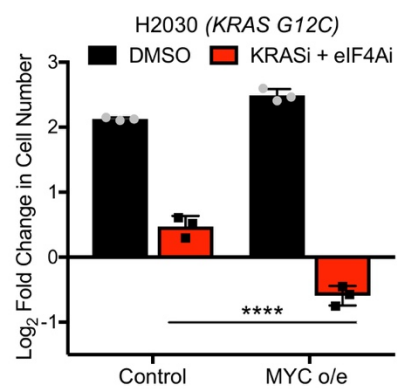
MYC copy number



- Deletion (5.3%)
- Diploid (30.7%)
- Gain (56%)
- Amplification (8%)

KRAS mutant NSCLC

Supplemental Figure 7. *KRAS*-mutant lung adenocarcinoma tumors frequently possess *MYC* copy number gain. *MYC* copy number for 75 *KRAS*-mutant NSCLC tumors is reported as deletion, diploid, copy number gain, or amplified.



Supplemental Figure 8. MYC overexpression sensitizes resistant NSCLC cells to combined RAS pathway/eIF4A inhibitors. (Top) Bar graph depicting fold-change in cell number of resistant H2030 and A549 cells ectopically expressing control or *MYC* cDNAs treated for 72 hours with vehicle (DMSO) or combined 25 nM eFT226 (eIF4Ai) and either 100 nM MRTX849 (KRASi) or 50 nM trametinib (MEKi) (mean \pm SD, $n = 3$; **** $p < 0.001$; one-way ANOVA and Tukey's post hoc test). (Bottom) Immunoblots showing suppression of p-ERK and overexpression of MYC in response to specified treatments and *MYC* ectopic expression.